REMARKS

FORMAL MATTERS

Claims 48-56, 58-67, 69-72, 74-81 and 83-94 and 96-99 are pending and currently under examination after entry of the amendments set forth herein.

Claims 48-56, 58-67, 69-72, 74-81, 83-94 and 96-99 were rejected.

Claims 48, 62 and 84 are amended. Support for these amendments can be found throughout the application as originally filed and in the following exemplary locations: page 6, lines 14-15; and Examples 2-5.

No new matter is added.

INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement under 37 C.F.R. § 1.97 is filed herewith.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Enablement

Claims 48-56, 58-67, 69-72, 74-81, and 83-91 are rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully traverse the rejection as discussed below.

Applicants burden under §112, first paragraph, is to provide a disclosure containing sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test for enablement asks whether one reasonably skilled in the art could make or use the recited invention from the disclosures of the patent application coupled with information known in the art—without having to resort to undue experimentation. *United States v. Telectronics*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). In addition, a patent specification need not teach, and preferably omits, what is well known in the art. See, e.g., *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

As best understood by the Applicants, it is the position of the Office that the specification is enabling for sufentanil as a fentanyl congener, but does not reasonably provide enablement for fentanyl itself or any other fentanyl congener. Office Action dated November 19, 2008, page 3.

Applicants respectfully submit that the application as filed contains information sufficient to enable one skilled in the pertinent art to make and use the invention as presently claimed. Specifically, the

application as filed enables the delivery of a composition comprising fentanyl or a fentanyl congener such as sufentanil according to the claimed methods.

The specification describes specific formulations comprising fentanyl or a fentanyl congener. At page 19 of the application as filed, the specification describes the use of hydrophobic solvents which are suitable for use in fentanyl or fentanyl congener formulations due to the lipophilicity of fentanyl and fentanyl congeners. The specification also describes, at page 19, specific formulations comprising fentanyl or a fentanyl congener (generally as a base) and a low molecular weight (e.g., MW less than about 300 g/mol) alcohol. Specific concentrations for these formulations are also set forth, along with specific examples of suitable low molecular weight alcohols. The specification does not limit the described formulations to sufentanil, but instead provides sufentanil as an exemplary fentanyl congener which may be formulated in the manner described.

In addition, the specification describes specific implantation and delivery sites which may be used in connection with the claimed methods (e.g., pages 22-23), specific delivery periods (e.g., page 23), specific low volume rates of delivery (e.g., page 24), and specific delivery devices compatible with the delivery of fentanyl or fentanyl congener formulations (e.g., pages 25-30). The specification also describes specific methods by which a physician can select an appropriate dose of a fentanyl or fentanyl congener formulation for use according to the claimed methods (Example 1, pages 33-34).

Finally, the specification describes exemplary loading parameters for an implantable convective delivery system (Example 2, pages 34-35), specific formulations of an exemplary fentanyl congener (sufentanil) comprising benzyl alcohol or benzylbenzoate (Examples 3-4, pages 35-36), and an *in-vitro* method of testing the release profile of fentanyl or a fentanyl congener from an implantable convective delivery system (Example 5).

Thus, the instant specification provides exemplary formulations for fentanyl and fentanyl congeners, exemplary delivery sites, exemplary delivery periods, exemplary low volume delivery rates, exemplary dose selection methods, exemplary implantable convective delivery systems, and exemplary release profile testing methods. In view of this disclosure, one of ordinary skill in the art could have readily practiced the claimed methods using fentanyl itself or fentanyl congeners as described in the specification. Applicants respectfully submit that the level of experimentation required, if any, to practice the full scope of the claimed methods would not be undue.

Enablement

Claims 48-56, 58-62 and 92 are rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph.

According to the Office, the specification is enabling for sufentanil at a concentration of about 0.5 mg/ml to about 500mg/ml, wherein the composition is administered to the subject using an implantable convective delivery system, and sufentanil is delivered from the system at a low volume rate of about 2ml/day. The Office asserts, however, that the specification does not reasonably provide enablement for sufentanil at any concentration other than between 0.5 mg/ml and 500 mg/ml delivered at a low volume rate. Office Action dated November 19, 2008, page 3.

Applicants respectfully disagree. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended independent claim 48 to recite that "the fentanyl or fentanyl congener is present in the composition at a concentration of *about 0.5 mg/ml to about 500 mg/ml.*" It is believed that this amendment is sufficient to address the rejection set forth by the Office. Withdrawal of the rejection is thus respectfully requested.

Written Description

Claims 48-56, 58-67, 69-72, 74-82, 83, 92, 93, and 96-99 are rejected as allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph, because the specification allegedly gives no guidance to one of ordinary skill in the art regarding the expressions "less" or "greater" as used in the claims.

Applicants respectfully disagree. However, solely in the interest of expediting prosecution of the instant application, Applicants have amended the claims to remove the terms "less" and "greater." In view of these amendments, it is believed that the rejection set forth by the Office has been adequately addressed. Withdrawal of the rejection is thus respectfully requested.

Furthermore, while claim 82 is included in the above rejection, it is noted that claim 82 was previously canceled.

REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 84-91 and 94 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over the article "Level Concept of Analgesic Dosing in Intensive Care Medicine with Sufentanil" by Wappler et al. (Anasethesiol Intensivmed Notfallmed Schmerzther (1998) 33(1):8-26: henceforth "Wappler") in view of

the article "Long-Term Spinal Opioid Therapy in Terminally Ill Cancer Pain Patients" by Wagemans et al. ("henceforth "Wagemans"). Applicants respectfully traverse the rejection as indicated below.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations.[1] Furthermore, as indicated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, it will often be necessary "to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue."[2] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[3] Finally, in *KSR* the Court held "[w]hen the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious."[4]

The proposed combination fails to teach or suggest each and every claim element

As best understood by Applicants, it is the position of the Office that Wappler teaches continuous infusion of sufentanil at a dose of 4.5 µg/hr to 150 µg/hr and that Wagemans teaches long-term opioid therapy with minimal side effects and efficacy throughout the body for different types of pain. According to the Office, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered at a concentration of 4.5 µg/hr to 150 µg/hr as allegedly disclosed by Wappler, and deliver sufentanil using an implantable infusion pump as allegedly disclosed by Wagemans.

Applicants respectfully submit that the proposed combination of Wappler and Wagemans fails to teach or suggest at least the following element of claims 84-91 and 94: "the composition is delivered from the system for 48 hours or more *at a low volume rate from about 0.01 µl/day to about 2 ml/day* and is sufficient to deliver from about 0.01 µg/hour to about 200 µg/hour of the sufentanil to the subject . . . ."

There is no disclosure in Wappler to indicate a low volume delivery rate, much less a low volume rate from about 0.01 µl/day to about 2 ml/day as recited in the instant claims. Instead, Wappler merely discloses the delivery of sufentanil via infusion pump at specific concentration based delivery rates to treat pain. This lack of disclosure with respect to a required claim element cannot be taken as a suggestion to include such an element in the proposed combination. Moreover, the addition of Wagemans fails to

[1] See *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007)
[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).
[3] *Id.* at 1741.
[4] *Id.* at 1740.

cure the deficiency in Wappler with respect to the claimed low volume delivery rate. Wagemans teaches long term opioid therapy with minimal side effects. However, there is no disclosure in Wagemans with respect to a low volume delivery rate of about 0.01 µl/day to about 2 ml/day. As with Wappler, this lack of disclosure with respect to a required claim element cannot be taken as a suggestion to include such an element in the proposed combination.

In contrast, the instant specification, in addition to disclosing the above delivery rates, specifically discloses high-concentration sufentanil formulations which facilitate the extended delivery of sufentanil at a low volume per unit time. See, for example, the instant specification at page 35, line 10 – page 37, line 25.

No apparent reason to combine Wappler and Wagemans

The Applicants respectfully submit that there would have been no apparent reason for one of ordinary skill in the art to combine the disclosed delivery rates of Wappler in the continuous infusion method described by Wagemans. This is because Wagemans solves the problem of providing analgesia in a subject in a completely different manner than that employed by Wappler.

Specifically, Wagemans describes spinal, i.e., ***local administration*** of opioids. Wagemans teaches that an advantage of spinal administration is that opioids act directly at the spinal cord level by binding to specific opioid receptors in the dorsal horn of the spinal cord.[5] Thus, the opioid, e.g., sufentanil, is delivered directly to the receptors it will act upon. Accordingly, Wagemans states: "The normal dosage of spinal opioids is considerably lower than <u>systemic</u> opioid dosage, therefore producing fewer side effects."[6] Thus, Wagemans does not teach or suggest systemic administration of sufentanil as currently claimed, because to do so would defeat Wagemans stated purpose of providing analgesia via local administration to the spine.

Wagemans indicates that in epidural administration "*systemic <u>adsorption</u>*" occurs in addition to penetration of the dura matter and arachnoid. However, Wagemans clearly teaches that epidural administration is local administration in the context of opioid delivery. By way of example, Wagemans indicates that the advantages of spinal administration (e.g., epidural administration) include "the ability to reach higher concentrations of opioids at the receptor site ***when compared with systemic administration***."[7]

[5] Wagemans page 71, left column.
[6] *Id.* (emphasis added).
[7] *Id.* (emphasis added).

In contrast, Wappler does not describe the local administration of opioids to the spine. Wappler does not explicitly indicate the route of administration used. However, Wappler does suggest that the drug is delivered ***intravenously***, i.e., systemically. Specifically, Wappler indicates that "some authors recommend the continuous giving of the drugs via ***syringe pumps.***"[8] As an example, Wappler refers to reference no. 1, which is an article entitled "*Analgesia and Sedation in Intensive Care*" by Aitkenhead, A.R. *Br. F. Anaesth.* (1989) 63:196-206. Aitkenhead describes its method of administration as follows:[9]

METHOD OF ADMINISTRATION

Most sedative and analgesic drugs are administered parenterally in the ICU. Sedation is achieved most satisfactorily by continuous i.v. infusion, a technique which avoids the peaks and troughs of analgesia and sedation associated with the use of intermittent i.m. or i.v. administration. The rate of infusion should be tailored to the patient's requirements, and usually requires adjustment from time to time. It is usually preferable to initiate sedation with a relatively rapid infusion, rather than by a bolus dose which may result in undesirable cardiovascular depression.

Thus, the reference cited by Wappler as showing continuous administration via ***"syringe pump"*** is a reference in which the administration is by continuous i.v. infusion. Wappler goes on to describe its method of administration as one which utilizes a "***syringe pump***."[10] Furthermore, in discussing their results in the context of previous studies, Wappler et al. specifically refers to references in which sufentanil was administered ***intravenously***. See, for example, the second paragraph of the Discussion section in Wappler, wherein Bailey et al. (1990) *Anesth. Analg.* 70:8-15 is cited and described. Bailey et al. describe their administration as follows:[11]

The magnitude and duration of analgesia and respiratory depression induced by fentanyl (1.0, 2.0, and 4.0 micrograms/kg) and sufentanil (0.1, 0.2, and 0.4 microgram/kg) after intravenous administration over 30 s were measured in 30 healthy young adult male volunteers divided into three groups and studied in a double-blind, randomized fashion. Each volunteer received one dose of fentanyl or sufentanil and no sooner than 48 h later, the corresponding equipotent dose of the other opioid.

[8] *See* the second paragraph of the Introduction in the translation of the full text Wappler et al. document (provided with the RCE filed Aug. 26, 2008) (emphasis added).
[9] Aitkenhead *Br. F. Anaesth.* (1989) 63:196-206, page 198 (provided in the Information Disclosure Statement filed herewith).
[10] See page 3 of the English translation of the full text Wappler et al. document (provided with the RCE filed Aug. 26, 2008).
[11] Bailey et al. (1990) *Anesth. Analg.* 70:8-15 (Abstract provided in the Information Disclosure Statement filed herewith).

In view of the above, Wappler suggests intravenous systemic delivery rather than local spinal delivery as described in Wagemans.

As evidenced by Wagemans, one of ordinary skill in the art would not normally apply a dosage of sufentanil suitable for intravenous administration in the context of local spinal delivery because in local spinal delivery the sufentanil is delivered directly to the receptors it will act upon. Thus, one of ordinary skill in the art would have no apparent reason to apply the dosage regime of Wappler in the context of the local spinal delivery described by Wagemans.

In view of the above, Applicants submit that the proposed combination of Wappler and Wagemans fails to render any of claims 84-91 and 94 *prima facie* obvious.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-007CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: March 19, 2009 By: /Michael B. Rubin, Reg.No.61231/

Michael B. Rubin
Registration No. 61,231

Date: March 19, 2009 By: /Carol L. Francis, Reg.No.36513/

Carol L. Francis, Ph.D.
Registration No. 36,513

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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